therapies, all likely contribute to the improved outcomes of cardiac patients receiving rehabilitation services, it is not possible to identify the contributions of individual components of cardiac rehabilitation to cardiovascular benefit, although exercise training, with its diverse favorable physiologic outcomes, including the beneficial effect on autonomic cardiovascular regulation, likely plays a pivotal role.

***Nanette K. Wenger, MD**

*Professor of Medicine (Cardiology)
Emory University School of Medicine
49 Jesse Hill Jr. Drive
Atlanta, Georgia 30303
E-mail: nwenger@emory.edu

doi:10.1016/j.jacc.2008.06.031

REFERENCES

1. Wenger NK. Current status of cardiac rehabilitation. J Am Coll Cardiol 2008;51:1619–31.
2. Wenger NK, Froelicher ES, Smith LK, et al. Cardiac rehabilitation. Clinical practice guideline no. 17. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research, and the National Heart, Lung, and Blood Institute, AHCPR Publication No. 96-0672; October 1995.

Editor's Note

In the August 5, 2008 issue of *JACC* the below Letter to the Editor was published with the incorrect Reply. Below please find the correct matching Letters and Replies addressing the manuscript "Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution" published in the February 12, 2008 issue of *JACC*. The editors regret the error.

Plaque Rupture: Plaque Stress, Shear Stress, and Pressure Drop

We read with interest the article by Fukumoto et al. (1) in a previous issue of the *Journal*. They used 3-dimensional intravascular ultrasound and computational fluid dynamics (CFD) to study wall shear stress (WSS) distribution in arteries with ruptured plaques. Their results showed that there are local elevations of WSS concentrations at proximal sites in the plaques and that these correspond to the rupture sites.

We want to emphasize that WSS is calculated as blood viscosity multiplied by the derivative of flow velocity with respect to the distance from the vessel wall ($\tau = \eta \times \partial u/\partial y$). Flow velocity varies along the stenotic artery across the plaque as the lumen narrows. Generally the maximum WSS should be at the location of the maximum stenosis, where the velocity is the highest and the lumen diameter is the smallest. There should not be any local elevation of WSS concentration if the lumen surface is smooth and there are no bad mesh elements. The use of image-based CFD can often cause problems with the geometry reconstruction and mesh generation. WSS is largely dependent on the geometry. Therefore, any effort to improve the model reconstruction and mesh generation is useful to improve the accuracy of the WSS calculation.

Pressure distribution across the stenosis is not shown in the article (1); it is not clear how pressure boundary condition was given in this study, but it is thought to be more important for plaque vulnerability. There is a pressure drop across the plaque because of the stenosis. According to the Bernoulli principle, this increased blood velocity produces a lower lateral blood pressure acting on the plaque. Thus, a pressure gradient build-up is created across the plaque that could rupture it. Any increase in systemic pressure or increase in the narrowing of the lumen would further increase the velocity through the narrowed lumen and increase the pressure drop. Furthermore, the magnitude of the pressure drop is much higher than the WSS. It can be tens to hundreds of times the magnitude of WSS for different degrees of stenosis.

Plaque stress (stress within the plaque) may be a more important factor when the mechanism of plaque rupture is considered. The arterial wall continuously interacts with hemodynamic forces, which include WSS and blood pressure. Plaque stress is the result of external hemodynamic forces. Plaque rupture itself represents structural failure of a component of the diseased vessel, and it is therefore reasonable to propose that the biomechanical properties of atheromatous lesions may influence their vulnerability to rupture. Recognizing which features contribute to this increased vulnerability may improve risk stratification and allow aggressive interventions to be targeted at patients with plaques that are prone to rupture. Therefore, when we model the mechanical process of plaque rupture, we need to look at the plaque stress and compare plaque stress with plaque material strength limit. We previously used a blood flow and plaque interaction model and demonstrated that fibrous cap thickness is critical to plaque stability (2). In this study, we also found that plaque stress in often higher at the shoulder regions at the proximal part of the plaque, and this is where plaque rupture can often be found.

***Zhi-Yong Li, PhD**
Jonathan H. Gillard, MD

*University Department of Radiology
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge CB2 0QQ
United Kingdom
E-mail: ZYL22@cam.ac.uk

doi:10.1016/j.jacc.2008.08.004

REFERENCES

1. Fukumoto Y, Hiro T, Fujii T, et al. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. J Am Coll Cardiol 2008;51:645–50.
2. Li ZY, Howarth SP, Tang T, Gillard JH. How critical is fibrous cap thickness to carotid plaque stability? A flow-plaque interaction model. Stroke 2006;37:1195–9.

Reply

We would like to express our gratitude to Drs. Li and Gillard for giving us their honest comments regarding our article (1). The key points of their criticism were: 1) we have to recognize the inherent limitations of computational fluid dynamics; and 2) we should consider the degree of stenosis, pressure distribution across the stenosis, as well as in-plaque stress, all of which may be more important in plaque rupture. We agree entirely with these comments.

Any kind of computational analysis, especially for life systems, requires many assumptions and hypotheses. To ensure its validity, all we can examine is the correspondence between the calculated results and the real-world data. The location of shear stress concentration obtained by our program, which is commercially available, corresponded almost exactly to the real location of plaque rupture. It may be true that the maximum shear stress should be at the location of the maximum stenosis; however, it comes to effect only if the cross-sectional lumen is circular or uniform in shape. The lumen shapes we analyzed were much more complicated, having non-negligible side branches, and the top of plaque hill usually did not correspond to the maximum stenosis. Furthermore, shear stress is dependent on not the peak value but the maximum "derivative" of flow velocity with respect to the distance from the vessel wall. Even if our data did not indicate the real shear stress, our method can still be useful for predicting the future rupture point.

Regarding other critical factors in plaque rupture, such as wall-distending pressure, the degree of stenosis, and in-plaque stresses, we responded to the previous letter to the editor (2). In addition to their work in 2006 (3), we also published an article in the *Journal* in 2005 (4) demonstrating the importance of fibrous cap thickness, lipid core, and calcification in plaque rupture. Wall-distending pressure or in-plaque stress may be much more important in driving the plaque rupture, because the degree of shear stress is very small compared with such forces. Therefore, we think that the local elevation of shear stress might become a trigger rather than a major driving force of plaque rupture. When one attempts to tear a thin paper into 2 parts, just stretching the paper is not sufficient. However, if one makes just a tiny cut in an edge of the paper, it will tear it very easily. We think that the local elevation of shear stress might form such a tiny cut-line, which may be derived from the modification of endothelial cell functions.

In our study (1), we demonstrated just such a statistical relationship between shear stress and plaque rupture. We are under the impression that plaque rupture is a multifactorial multiprocess as well as multi-interaction phenomenon that is deterministic in some ways and stochastic in others.

***Takafumi Hiro, MD, PhD, FACC**
Yusaku Fukumoto, MD, PhD
Takashi Fujii, MD, PhD
Masunori Matsuzaki, MD, PhD, FACC

*Division of Cardiology
Department of Clinical Science of Medicine
Yamaguchi University Graduate School of Medicine
1-1-1 Minami Kogushi
Ube, Yamaguchi 755-8505
Japan
E-mail: thiro@yamaguchi-u.ac.jp

doi:10.1016/j.jacc.2008.06.033

REFERENCES

1. Fukumoto Y, Hiro T, Fujii T, et al. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. J Am Coll Cardiol 2008;51:645–50.
2. Hiro T, Fukumoto Y, Fujii T, Matsuzaki M. Local blood pressure rather than shear stress should be blamed for plaque rupture (reply). J Am Coll Cardiol 2008;52:500.
3. Li ZY, Howarth SP, Tang T, Gillard JH. How critical is fibrous cap thickness to carotid plaque stability? A flow-plaque interaction model. Stroke 2006;37:1195–9.
4. Imoto K, Hiro T, Fujii T, et al. A computational analysis of stress distribution using vessel models and three-dimensional intravascular ultrasound imaging. J Am Coll Cardiol 2005;46:1507–15.

Local Blood Pressure Rather Than Shear Stress Should Be Blamed for Plaque Rupture

A recent article (1) published in the *Journal* corroborates the hypothesis that shear stress triggers fibrous cap rupture. In 20 patients with considerable lumen narrowing (maximum area reduction of 80 ± 7%), ulcerative plaque rupture preferentially occurred in areas with locally high wall shear stresses (WSS), estimated by means of computational modeling. However, the authors of this study do not answer the basic question of whether local WSS distribution is indeed related to plaque rupture.

Hemodynamics is an interplay between pressure, flow, and morphology. The study by Fukumoto et al. (1) mainly considers the interaction between flow and morphology under steady-state conditions. Compared with an unaffected site, the increase in WSS around a plaque can be estimated to be a factor of 10 assuming simple circular geometries. For a normal WSS of 0.6 Pa (2), the mean WSS within the stenosis will remain <10 Pa, which might be too low to initiate plaque rupture directly, as acknowledged by the authors.

The article does not fully appreciate the influence of local blood pressure within a stenosis, although this pressure was calculated as well. Let us consider the hemodynamics in the vicinity of a stenosis (3), where in a steady-state situation the sum of potential energy (local blood pressure) and kinetic energy (local blood velocity) is constant (Bernoulli equation): an increase in velocity induced by geometry decreases local pressure (3). An area reduction of 80% converts to an increase in velocity by a factor of 5, and the